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Mixed gonadal dysgenesis: whole life follow-up of a rare case

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There are two forms of gonadal dysgenesis – mixed and pure. In the mixed form, some differentiated gonads as well as some either ovarian or testicular rudiments are present. This form results in a number of phenotypes with a possibility of malignant transformation. In the pure form occurring in female gender, also some rudimental gonads are bilaterally present. In the case of simultaneous presence of Y chromosome, also some malignant transformation may appear (Siklar et al. 2007). Chromosomal aberrations are present in 2-7 % adult pairs with fertility disorders and in 0.6 % of newborns. However, only few cases with similar chromosomal aberrations were described so far (Roubin et al. 1977; Alexander et al. 1978; Teyssier et al. 1982; Caglayan et al. 2009).

Mixed gonadal dysgenesis presents as a unilateral testis, usually intraabdominal, also with a streak gonad on contralateral side, and persistent mullerian structures. 45X/45XY karyotype is the most frequent in such cases with predominance of 45X cells in both peripheral lymphocytes and gonads. We present a rare case of a left undescended testis, normally descended right testis, with penoscrotal hypospadias, who had a normal karyotype and whose histopathological findings were endometrial tissue and fallopian tube in left testicular biopsy. Gonadal dysgenesis should always be kept in mind because of a possibility of undescended testis and proximal hypospadias. If karyotype reveals a 46XY gonadal dysgenesis, these patients need the careful follow-up to screen for gonadoblastoma in remaining normal testis. Subjecting the patients to prophylactic orchidectomy with hormone replacement can be an additional option in such patients.

Case report

One patient aged 33 years with a mixed type of gonadal dysgenesis and with the karyotype 45X /46 X i(Yq) /47 X, i(Yq), i(Yq) is being presented. He was born on November 20, 1978 as a preterm child of 2250 g body weight and 47 cm body length. His external genitals showed several malformations such as the angulation of penis, periscrotal hypospadia, undescended testes and some palpable formation of peas grain size in the right inguinal channel.

At the age of two years (at 1980) a probatory laparotomy has been performed at which both inguinal channels were found empty. Small uterus of hazelnut size has been found which continued as some sack like formation firmly attached to the wall of the urinary bladder.

From such rudimental uterus some ligament like formations tended to both sides and small rounded formations were found at the end of each of them. Considering the karyotype of this patient (as presented above) and the histological examination of those formations (e.g. on the right side the testis has been found, while on the left side there was only the tissue of ovarian tube) it was decided to remove both of them because of the risk of malignant transformation.

In December 1998, increased urinary excretion of 17-ketosteroids (2.04 mg/24 h) and pregnanetriol (0.22 mg/kg body weight, while normal value is 0.04 mg/kg) was found. Considering these findings, possible

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congenital adrenal hyperplasia has been suspected which, however, was later excluded. External genitals were corrected by repeated plastic surgeries. Over time, with increasing age also some somatic signs of "Turner's syndrome type" started to appear such as retarded body growth, "sphinx like face", pterygium colli, lower ear shells, shield like thorax, double right kidney. Since his body growth has been continuously retarded, the attention has been also focused to the possibility of growth hormone deficiency. At that time, the routine insulin test showed a subnormal response, maximum increase of GH level being 7.6 ng/ml. Thus, partial GH deficiency has been detected and GH supplementation was carried out since 1992 until 1998, when the GH response to insulin was found normal as well as that in 2011 (Table 1). In addition, because of his hypogonadism the substitution by testosterone (3-oxoandrosterone, Nebido-Bayer Schering Pharma AG) 1000 mg/4 ml every 3 months has been started since 1998 (at the age of 20 years).

The true hermaphroditism appears extremely rare, since it is including those individuals which are possessing both the testes and ovaria, e.g. either the testis on one side and the ovary on the other or unilateral "ovotestis" on one side and normal gonads (or a second "ovotestis") on the other. Such type of hermaphroditism has been also present in our patient. At this occasion, it should be also noted that such patients may also be fertile.

There are several recommendations for the diagnostic steps and treatment. First, detailed familiar history should be obtained including the questions about a "doubled gender", infertility, unexpected changes during the puberty. The attention should be also paid to possible preterm delivery and abortuses, taking possible teratogenic drugs by the mother during pregnancy and possible virilization of the mother by androgen producing tumor (Marzotto Caotorta et al. 1998). The attention should be also paid to the examination of external genitals as well as of the rectum. Among the laboratory and genetic examinations great

Table 1

Comparison of data obtained by i.v. insulin test between 1998 and 2011 (1998/2011)

Time after Insulin injection (min)	Growth hormone (ref. 0.0 - 3.0 μg/l)	Glycemia (ref. 4.0 - 5.5 mmol/l)	IGF* (ref. 115 - 307 ng/ml)
0	0.17 / 0.12	4.66 / 4.93	145 / 163
30	0.23 / 4.29	1.38 / 2.74	
45	0.39 / 16.8	1.38 / 2.74	
60	10.16 / 15.5	1.93 / 2.25	
90	11.52 / 16.10	2.10 / 2.24	

* IGF = insulin like growth factor

Table 2

Data on hormone levels in the patient between 1990 and 2011

	1990	2004	2005	2006	2007	2008	2011
LH (1.7 – 8.6 IU/l)	16.5					14.8	18.2
FSH(1.5 -12.4 IU/l)	94.6					40.3	45.2
TST (10 - 28 nmol/l)	7.9	10.8	11.3	9.8	9.5	22.8	25.3
17-OH-P (1.5 -7.2 nmol/l)	0.35						1.9
Cortisol (nmol/l)	242						495.4
DHEAS (4.3 -12.2 μmol/l)							6.0
SHBG (16.5 -56.0 nmol/l)							58.5
FAI (35 - 92 %)							43.62
PRL (4.6 - 21,5 μg/l)							43.6

Legend: LH = luteinizing hormone; FSH = follicle-stimulating hormone; TST = testosterone; TSH = thyroid stimulating hormone; fT4 = free thyroxine; 17-OH-P = 17-hydroxy-progesterone; DHEAS-dehydroepiandrosterone; SHBG- sex hormone binding globulin; FAI – free androgen index; PRL- prolactine

attention should be paid to chromosomal examination, complete endocrine tests, including the examination of electrolytes and 5-alpha reductase type II (Jaubert et al. 2004). Special role is also played by the examination of kidneys by ultrasound, identification of internal genitals, genitoghraphy, CT and MR examination. The treatment should be conducted by multidisciplinary supervision of the genetician, endocrinologist, surgeon and urologist (Sharma et al. 2008).

In summary, presented patient had atypical form of mixed gonadal dysgenesis associated with a chromosomal aberration resulting in a mixed gonadal dysfunction which is a rare form of the true hermaphroditism. He has been subjected to repeated surgical interventions during the childhood including the plastic of genitalia. Since the deficiency of growth hormone has been found, he was supplemented by this hormone until the age of 20 years. However, the mechanism of temporary GH deficiency during the adolescence remained unexplained, since a satisfactory level of GH appeared at the adulthood. In addition, the previous GH deficiency has not been accompanied by any deficiency of other pituitary hormones (such as luteinizing hormone, follicle-stimulating hormone or prolactin). Somatic development of this patient resembled the Turner's syndrome in which also GH deficiency occurs. In this patient, the long term continuing testosterone treatment has been started after the age of 20 years because we preferred to wait for the increase of body height as much as possible.

It should be stated that, in such a case of rare malformation, early diagnosis contributed to the surgical correction resulting in the removal of potential malignant transformation of the tissue and rendered possible the definition of genital organs as appropriate to the gender. Androgen substitution then supported the expression of male phenotype.

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